Decoding the Role of Genetic Biomarkers in Neurodegenerative Diseases: Dysregulations of RNA Binding Protein Aggregations and Molecular Pathophysiologies

Exploring Commonalities Between Atypical Parkinson's Disease and Small Fiber Neuropathy and Utilizing Artificial Intelligence Applications

Dr. Sheryene Tejeda MD PhD MHS MFS

Medicinal Technologies, Palm Beach Gardens, USA

Introduction

Neurodegenerative diseases, characterized by the progressive degeneration and dysfunction of neurons, present significant clinical challenges, with many conditions ultimately proving fatal. Over the past few decades, extensive research has focused on developing and validating biomarkers to improve diagnosis and treatment. The repertoire of biomarkers for central nervous system (CNS) diseases has expanded to include a diverse array of biofluids, nucleic acids, and imaging modalities. However, while imaging and tissue biopsy-based indicators continue to evolve, RNA and protein biomarkers are emerging as crucial tools in the early detection and management of these diseases.

It is critical examine the key genetic biomakers, including microRNA (miRNA), long noncoding RNA (lncRNA), circulating miRNA (cimiRNA), and proteins, which holds promise for improving diagnosis and management of neurodegenerative diseases. In addition, it highlights the impending challenges related to integrating novel biomarkers into clinical practice and research.

One goal is to reduce the time, patient suffering, and cost associated with screening for neurodegenerative diseases and support identification of therapies toward improving the quality of life for patients with neurodegenerative diseases.

Parkinson's Disease and Small Fiber Neuropathy

Parkinson's disease (PD) is a well-recognized neurodegenerative disorder that primarily affects the central nervous system. The pathogenesis of PD is closely linked to the accumulation of alpha-synuclein (α-Syn) in Lewy bodies (LBs) within the brain. Genetic mutations, such as those in the SNCA gene, as well as duplications or triplications of the SNCA locus, are known to precipitate familial forms of PD. These genetic alterations result in elevated α-Syn levels in both the brain and peripheral tissues, contributing to the neurodegenerative process. Other genetic factors associated with PD include mutations in LRRK2, GBA, and DJ-1.

Small fiber neuropathy (SFN), a type of peripheral neuropathy characterized by pain and sensory disturbances, is increasingly recognized as a co-morbidity in PD. SFN manifests with acute pain episodes, often beginning in the extremities and potentially spreading to other regions. Diagnosis typically involves skin biopsy, with intraepidermal nerve fiber density (IENFD) as a reliable measure, showing a diagnostic sensitivity ranging from 81% to 88%. Studies have demonstrated a higher prevalence of SFN among PD patients, with nerve fiber degeneration patterns in skin biopsies reflecting the central neurodegeneration observed in the substantia nigra, suggesting shared underlying pathophysiological mechanisms.

Intraepidermal nerve fiber density (IENFD) is a highly accurate method for assessing the loss of nerve fibers in the skin, particularly for diagnosing SFN. Numerous studies have demonstrated a significant reduction in IENFD in patients with Parkinson's Disease (PD). These studies utilized immunostaining with the pan-axonal marker protein gene product 9.5 (PGP9.5) to evaluate nerve density. Our research also observed reduced IENFD and small ocular nerve fiber density in subjects with Parkinson's disease, highlighting a connection between these findings, autonomic dysfunction, and the sensation of emotional contact.

Methods

To prepare this review, we conducted a literature search using terms such as "small fiber neuropathy," "biomarkers," "diagnosis," "diagnostic tools," and "diagnostic tests." The search was limited to human studies published between 2010 and 2011, a period marked by the publication of European Federation of Neurological Societies/Peripheral Nerve Society guidelines on the use of skin biopsy for SFN diagnosis. We adhered to strict criteria for SFN validation via biopsy to ensure the inclusion of high-quality studies.

Therapeutic Approaches in Neurodegenerative Diseases

Therapeutic interventions for neurodegenerative diseases encompass a wide range of modalities, including pharmacological treatments, physical therapies, and surgical procedures. Current therapies primarily focus on managing symptoms and slowing disease progression, with a notable shortage of curative options. The identification and validation of diagnostic biomarkers are crucial for developing new therapeutic strategies and improving the precision of existing treatments.

Biomarkers offer immense promise for improving the diagnosis and treatment of CNS diseases. They facilitate early disease detection, enhance diagnosis accuracy, and facilitate the creation of personalized treatment programs suited to the specific needs of individual patients [10]. Biomarkers, measurable signals providing information on normal and pathological processes within the brain and spinal cord, can be identified in a wide variety of biological samples, including blood, cerebrospinal fluid (CSF), urine, and saliva, and through imaging methods [11, 12].

Biomarkers are necessary for advancing successful therapeutics that modify illnesses [13] and improving diagnostic methods in clinical settings. They play a pivotal role in diagnosing, monitoring, and evaluating the success of treatments for several neurological conditions, including Alzheimer's disease, multiple sclerosis, and Parkinson's disease [2, 14–16]. The use of biomarkers enhances the understanding and treatment of neurological disorders, contributing to the ongoing efforts to improve both the management and comprehension of neurodegenerative diseases.

Also known as biostatistical indicators, biomarkers serve as vital indicators of both normal and abnormal biological processes. Through the examination of particular alterations in pathologies, biochemistries, and genetics, researchers gain comprehensive insights into the characteristics of various diseases. Effective biomarkers must distinguish between diseases of interest and other conditions, predict the likelihood of disease, aid in early detection, and guide the development of new therapeutic drugs.

Recent technological advancements have enabled the identification of biomarkers linked to a wide range of neurodegenerative diseases. Notable examples include phosphorylated tau protein and aggregated β-amyloid peptide for Alzheimer's disease (AD), α-synuclein containing Lewy bodies and altered dopamine transporter (DAT) imaging for Parkinson's disease (PD), SOD mutations for familial amyotrophic lateral sclerosis (ALS), and CAG repeats produced by Huntington's gene mutations in Huntington's disease (HD). This review focuses on the latest findings related to biomarkers connected to the four neurodegenerative illnesses that have been brought to light.

Role of SCN9A and SCN10A Gene Mutations in Small Fiber Neuropathy

Mutations in the SCN9A or SCN10A gene may contribute to the development of SFN. These genes encode alpha subunits of sodium channels, specifically NaV1.7 (SCN9A) and NaV1.8 (SCN10A), which are critical for transmitting electrical signals in nerve cells.

Nociceptors, responsible for pain signal transmission to the brain and spinal cord, rely on these sodium channels. Mutations in SCN9A can lead to altered NaV1.7 channels, resulting in channels that do not close properly, allowing excess sodium ions to enter nociceptors. Similarly, mutations in SCN10A can cause NaV1.8 channels to open more easily, further increasing sodium ion influx.

This increased sodium ion presence in nociceptors heightens sensitivity to stimuli that normally wouldn't cause pain, leading to exaggerated pain responses. Over time, this continuous influx can cause the degeneration of axons that transmit pain signals, contributing to the symptoms of SFN. This condition is characterized by fluctuating symptoms, such as heightened pain sensitivity, temperature dysregulation, and abnormal pain sensations.

Studies indicate that approximately 30% of individuals with SFN have mutations in the SCN9A gene. The progression of SFN involves the degeneration of pain-transmitting fibers, leading to a disease presentation that can vary significantly over time.

Biomarker-Based Diagnostics in Small Fiber Neuropathy

Advancing the understanding of neurodegenerative mechanisms in Parkinson's disease (PD) necessitates research into both central and peripheral processes. PD-related neurodegeneration often presents asymmetrically, primarily affecting one hemisphere of the brain. It is, therefore, crucial to investigate whether this asymmetry extends to the peripheral nervous system. Previous studies using skin biopsy and PGP9.5 immunostaining have indicated increased neurodegeneration on the more affected side, though these studies were limited by their focus on a single staining method, which constrained the ability to assess asymmetric regeneration.

Peripheral nerve fibers are classified by size and function. Large fibers include myelinated Aα and Aα/β fibers, are responsible for controlling motor and sensory processes. In contrast, small nerve fibers, including unmyelinated C fibers and thinly myelinated Aδ fibers, are responsible for controlling temperature perception, pain, and autonomic functions. Patients with small fiber neuropathy (SFN) experience damage to both the Aδ and C fibers, leading to neuropathic pain (NeP), burning in the limbs, and autonomic dysfunction due to the diverse functions of small fibers. Recent advancements in understanding the mechanisms underlying NeP in SFN have highlighted the role of transient receptor potential vanilloid subtype 1 (TRPV1). Identified in 2006 as a key player in painful neuropathies, TRPV1 is localized to the keratinocytes in SFN patients. Its neurotoxin-induced depletion triggers the overexpression of various biological substances and receptors, initiating a complex cascade of cellular signaling alterations.

Small fiber neuropathy (SFN) is a prevalent neurological disorder, with an estimated incidence of 52.95 per 100,000 people. However, this figure is likely a significant underestimate due to the challenges associated with diagnosing the condition. Research suggests that SFN may account for as much as 40% of fibromyalgia syndrome cases, implying that the global prevalence of SFN could approach 100 million people.

In approximately 50% of SFN cases, the cause remains unknown. Nonetheless, common secondary causes include autoimmune diseases, diabetes, amyloidosis, sarcoidosis, exposure to toxic chemicals, and vitamin B12 deficiency. The current therapeutic approach for idiopathic SFN (iSFN) primarily involves symptomatic relief using non-opioid and opioid analgesics, antidepressants, and antiepileptic drugs. While these treatments may alleviate symptoms, they do not address the underlying pathophysiology of iSFN and are associated with risks such as drug dependence, adverse side effects, and potential opioid misuse with prolonged use.

Given these limitations, identifying biomarkers is crucial for screening occult causes in patients with initially idiopathic SFN (iiSFN), especially in those without recognized risk factors. Early detection of underlying causes in patients with iiSFN could enable therapy at an earlier stage, which can significantly improve the quality of life of patients, particularly young patients. Early intervention might also stimulate axonal regeneration, which can alleviate or even cure patients' symptoms since peripheral axons continue to develop throughout a person's lifetime. A study on patients with mixed polyneuropathies found that disease-modifying treatment adjustments were implemented in 25% of cases following screening. Therefore, it is recommended that iiSFN patients undergo screening for prevalent occult causes of the condition.

The widespread occurrence of SFN and debilitating effects, regardless of specific etiology, underscores the importance of identifying biomarkers in stratifying patients and developing cause-centered therapies. According to the Dictionary of Biomarkers, Endpoints, and Other Tools (BEST), a biomarker is a distinguishing property that is quantified as an indicator of normal biological processes, pathogenic processes, or reactions to an exposure or intervention, including therapeutic treatments. Biomarkers can serve several roles, including susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety indicators. In this context, SFN biomarkers can more accurately identify patient groups and could be used as diagnostic tests to tailor treatment strategies to the specific causes of SFN.

The utility of SFN biomarkers is influenced by factors such as geographic region, ethnicity, genetics, and environmental context, as well as patient demographics like age. For instance, a study in the Czech Republic involving 84 patients identified diabetes mellitus (DM) as the

most prevalent and significant risk factor for SFN (odds ratio = 3.6, P = 0.009). In contrast, research conducted in the United States found that the most prevalent causes of SFN were idiopathic (73%), assumed hereditary (18%), and diabetes (10%). In the Netherlands, the largest cohort study to date, involving 921 participants, associated pure SFN with autoimmune diseases, sodium channel (SCN) gene mutations, diabetes, glucose intolerance, and vitamin B12 deficiencies, in order of prevalence. SFN is also common among generally healthy children and young adults, where it is often associated with inflammatory or dysimmune processes.

SFN considerably diminishes a patient's quality of life, both physically and psychologically. Due to the variability of the condition, diagnosing SFN, identifying its causes, selecting treatment options, and predicting prognosis are all challenging. Thus, biomarkers can offer substantial benefits in managing these elements and treating the underlying causes of SFN.

Benefits of Artificial Intelligence in Researching Genetic Biomarkers

Artificial intelligence can potentially decrease the required number of subjects for a clinical study. From the initial data of an experimental patient, researchers may utilize the twin to forecast the future progression of the identical patient in the control group and compare the resulting outcomes. Typically, this approach decreases the required number of control patients by a range of 20% to 50%. Utilizing this approach permitted a more extensive trial and data capturing to compare the commonalities observed in Parkinson’s and SFN.

Additionally, the implementation of artificial intelligence potentially reduces the need for guessing and manual effort in improving eligibility criteria for clinical trials. Sometimes, even teams within the same organization and researching the same disease may develop divergent criteria for a clinical trial. An artificial intelligence system can produce a suitable set of criteria for, for example, body mass index. After determining the requirements for eligibility, researchers must locate patients who meet those criteria. Users may input inclusion and exclusion criteria in natural language or by entering a trial's identification number using a web-based interface. The application then converts the eligibility requirements into a formal database query to locate corresponding candidates in patient databases.

Facilitating the connection between researchers and patients not only accelerates clinical research but also, it enhances its resilience. Frequently, trials exclude certain populations but artificial intelligence can devise methods to incorporate them and still render valid results.

Conclusion

Small fiber neuropathy (SFN) is a complex and often debilitating condition with diverse etiologies and a significant impact on patient quality of life. The identification and application of biomarkers offer a promising approach to overcoming the diagnostic and therapeutic challenges associated with SFN. By facilitating early diagnosis, improving patient stratification, and enabling targeted therapeutic interventions, biomarkers have the potential to transform the management of SFN.

Future research utilizing artificial intelligence should focus on refining these biomarkers, expanding their clinical applicability, and exploring their role in predicting therapeutic outcomes. As the field advances, the integration of biomarker-based diagnostics into routine clinical practice will be essential for improving the diagnosis, treatment, and overall management of SFN and related neurodegenerative conditions, ultimately leading to better patient care and outcomes.

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